Baseline characteristics of a nationwide cohort of pediatric patients with acute leukemias of Down syndrome

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Summary

Purpose: Down syndrome (DS) or trisomy 21, brings together some unique aspects from clinical pediatrics. Among the hematological disorders present in DS, by far the most important is the predisposition for developing acute leukemia. Acute myeloid leukemia (AML) of DS has a preleukemic state with the onset in the neonatal period, rarely symptomatic but with the presence of blasts in peripheral blood smear and apparently a spontaneous remission. The unique tumor profile of DS underlines the importance of chromosome 21 in hematopoiesis and it can help understanding leukemogenesis in general. The purpose of this study was to present the very rare cases with DS and transient leukemia and/or acute leukemia that were found in a nationwide survey of Romania, in three centers of pediatric hematology and oncology.

Methods: A nationwide analysis of the very rare cases of transient leukemia of DS are described, involving the three major pediatric hematology centers of Romania: Cluj-Napoca, Bucharest and Timisoara. Data analysis was performed using R 3.5.3. Categorical variables were presented as absolute value (percent). Contingency tables were analyzed using the Fisher test. Normality of the distribution was assessed using the Shapiro test and histogram visualization, but also took into consideration the sample size. Non-normally distributed variables were presented as median (quartile 1, quartile 3). Wilcoxon test was used to determine the differences between two non-normally distributed groups. A p value under 0.05 was considered statistically significant.

Results: It appears that the more aggressive entity at presentation is represented by CD45 positive leukemia, which is the more frequent of the myeloid lineage and has lower counts at diagnosis.

Conclusion: We address this manuscript to pediatricians and neonatologists in order to emphasize the importance of diagnosing hematological disorders in children with DS, especially neonates, even if they are asymptomatic.

Key words: Down syndrome, acute leukemia, nationwide survey, baseline characteristics

Introduction

Down syndrome (DS) was first described by John Langdon Down in 1866 in a paper wrongfully called “Observations on an ethnic classification of idiots” [1]. The prevalence of DS is 1/700 births and has a positive correlation with the age of the mother [2,3]. Statistics from 2015 show that
in Romania the prevalence of people with DS per 10,000 inhabitants was 3.3%, with a total number of 4,414 persons with DS, most of them under 19 years old [4].

The chromosome 21 is responsible for the specific facial appearance associated with mental retardation and heart malformations (50%), gastrointestinal malformations (12%), visual (50%) and hearing problems (75%), endocrine disorders related to thyroid function (4-18%), predisposition to leukemia (1%), epilepsy (1-15%) and Alzheimer disease (4-55%) [5-7].

The onset of DS-related hematologic disorders takes place during intrauterine life, in the third trimester, with a dyserythropoiesis and dysmegakaryopoiesis responsible for the increased level of erythrocyte and megakaryocyte precursors in the liver [8]. After birth, this disorder of hematopoiesis will generate the predisposition to acute myeloblastic leukemia (AML) or acute lymphoblastic leukemia (ALL) for people with DS (AML-DS, ALL-DS), known to have a 10-20 folds higher risk of developing leukemia than the general population [9].

The World Health Organization (WHO) defines the presence of blasts in the peripheral blood smear of neonates with DS as transient leukemia of Down syndrome (TL-DS) [10]. The diagnosis is based on clinical data without any specifications for the number of blasts or the presence of GATA1 mutation. Most of the cases are asymptomatic or resolve before birth, making the prevalence of TL-DS hard to estimate [11]. The British Hematology Society provided in 2018 a guideline for TL-DS, defining this as the presence in the peripheral blood smear of neonates with DS of more than 10% blasts associated with GATA1 mutation and/or clinical criteria [12]. TL-DS is found only in neonates with DS, is different from congenital leukemias [13] and its unique feature is the spontaneous resolution in the majority of cases. However, TL-DS can’t be considered a benign disorder because some cases (10-20%) have a dismal outcome [14] or can develop in time AML. Risk factors for a bad outcome or early death are considered prematurity, organomegaly, increased level of white blood cells or blasts, liver involvement, coagulation disorders and absence of spontaneous remission [14-18]. Early death can be caused by liver failure, hydrops fetalis with cardiac-respiratory failure [19] and the mortality rate, in this case, is 9-10% [15,17].

Myelodysplasia has some unique features in people with DS [20]. About 4-10 % of neonates with DS have TL-DS [13,15,21], 20% of them will develop AML until the age of 4 years [14,16,20,22], the rest of them will have a spontaneous resolution in the first 3 months of life [23]. AML that appears in patients with DS until the age of 4 years is usually megakaryoblastic [24], has a good response to treatment and a favorable prognosis in 80% of the cases [25-27]. Although the mechanism of developing AML-DS after TL-DS is unknown, the presence of GATA1 mutation on the X chromosome of the patients that had TL-DS and then AML-DS, suggests a clonal development of AML-DS [28-30].

The transcription factor GATA1 has a central role in hematopoiesis and is encoded by the GATA1 gene from the X chromosome. GATA1 mutation results in the introduction of a premature stop codon in the gene sequence that encodes the amino-terminal activation domain. These mutations will provide the synthesis of a shorter variant of GATA1 that is initiated downstream. Short GATA1 (GATA1s) protein, which lacks the amino-terminal activation domain, binds DNA and interacts with its essential cofactor, friend of GATA1 (FOG1), but has a reduced transactivation potential [28]. GATA1 has a central role in the maturation of megakaryocytes and the survival of erythroid precursors [31,32]. Wechsler et al have identified the presence of GATA1 mutation in the blasts of patients with AML-DS. Furthermore, this mutation was also identified in the blasts of neonates with TL-DS [22,30,53,54], suggesting the theory that this mutation is an early event of DS-related myelodysplasia and that in some cases, the remission of TL-DS is just apparent and AML-DS results from a clone of TL-DS [29].

Recent data regarding DS showed that trisomy 21 is not enough to lead to all the disorders related to this syndrome. One specific example of this is the presence of GATA1 mutation in both TL-DS and AML-DS. Although many other genetic or epigenetic mutations have been identified since the discovery of GATA1, none of this can fully explain the mechanism of TL-DS and its progression to AML.

**Methods**

The purpose of this study was to describe the cases of DS related transient leukemia and/or acute leukemia found in the three major: centers of Pediatric Hematology from Romania: Cluj Napoca, Timisoara and Bucharest. This retrospective study was performed and we collected the clinical and laboratory data of patients with TL-DS and/or AML-DS or ALL-DS that were admitted in one of the Pediatric Hematology and Departments from the Clinical Institute Fundeni in Bucharest, Louis Turcanu Clinical Hospital for Pediatric Emergencies in Timisoara or the Clinical Hospital for Pediatric Emergencies in Cluj-Napoca. The study was performed after the written approval was obtained from the head of each department.
Statistics

Data analysis was performed using R 3.5.3. Categorical variables were presented as an absolute value (percent). Contingency tables were analyzed using Fisher test. The normality of the distribution was assessed using Shapiro test and histogram visualization but also took into consideration the sample size. Non-normally distributed variables were presented as median (quartile 1, quartile 3). Wilcoxon test was used to determine the differences between two non-normally distributed groups. A p value under 0.05 was considered statistically significant on log rank test.

Results

We included 20 patients with DS and AML or ALL and/or TL-DS. Five patients were diagnosed with AML-DS, 11 with ALL-DS and one patient for which data regarding the type of leukemia were missing because parents refused the bone marrow aspirate and the patient was lost to follow up. Two of the patient with AML-DS were diagnosed with TL-DS in the neonatal period. Also included in the study were 3 patients diagnosed at birth with TL-DS but without developing acute leukemia so far. The mean age for the onset of AML-DS was 2.4 years and for ALL-DS was 4 years. The mean age for the diagnosis of patients with TL-DS was 17 days (Table 1).

The diagnosis of TL-DS was based on clinical criteria and hematological changes including the presence of blasts in the peripheral blood smear. Three of 5 patients were born at term and 2 at 36 weeks of gestation, the mean weight at birth being 1480 g. Two had hepatosplenomegaly and one patient developed congestive heart failure and pericarditis and was known with an interventricular septal defect. Hematological changes were thrombocytopenia (2/5 patients), increased leucocytes (1/5 patients) and more than 10% blasts in the peripheral blood smear for all the patients. Immunophenotyping by flow cytometry was performed for two patients from the peripheral blasts. Both cases had positive markers of stem cells like CD34 and CD117 and positive markers for myeloid cells like CD33 and CD13. GATA1 mutation was not available for any patient. Four patients had spontaneous remission until the age of 3 months and for the fifth patient who presented with heart failure, treatment was required and remission was obtained at the age of 3 months. Two of the patients with TL-DS developed AML at the age of 1 year and 3 months and 3 years and 4 months, respectively.

Table 1. Patients with acute leukemia: clinical and laboratory findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (% )</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>F</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>3.20 (3-4.25)</td>
</tr>
<tr>
<td>Leukemia type, n (%)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>4 (25.00)</td>
</tr>
<tr>
<td>AMkL</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>9 (56.25)</td>
</tr>
<tr>
<td>B common</td>
<td></td>
</tr>
<tr>
<td>pre B</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td>Biphenotypic</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td>Cardiac malformations, n (%)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Clinical presentation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Hepato and/or splenomegaly</td>
<td>5 (31.25)</td>
</tr>
<tr>
<td>Purpura</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td>Pain</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td>Leukocytes (*10^3/uL)</td>
<td>6.45 (3.93-23.18)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.90 (6.15-10.08)</td>
</tr>
<tr>
<td>Erythrocytes (*10^6/uL)</td>
<td>2.80 (2.17-3.47)</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>85.6 (79.2-88.8)</td>
</tr>
<tr>
<td>MCH (g/dL)</td>
<td>34.6 (33.7-34.9)</td>
</tr>
<tr>
<td>Thrombocytes (*10^3/uL)</td>
<td>38.50 (19.25-67.75)</td>
</tr>
<tr>
<td>Peripheral blasts (percent)</td>
<td>12 (3-45)</td>
</tr>
<tr>
<td>Bone marrow aspirate blasts (percent)</td>
<td>80 (68-88)</td>
</tr>
</tbody>
</table>

Table 2. Patients with TL-DS: clinical and laboratory findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2 (40)</td>
</tr>
<tr>
<td>F</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Diagnosis age (days)</td>
<td>17 (10, 23)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38 (56, 38)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>2480 (2100, 3700)</td>
</tr>
<tr>
<td>Hepato and/or splenomegaly, n (%)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Hydrops</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serositis</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Hemorrhagic syndrome</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac abnormalities (cardiac insufficiency)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Hepatic abnormalities, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal abnormalities, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leukocytes (*10^3/uL)</td>
<td>35.6 (22.8, 44.4)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>17.0 (15.8, 18.9)</td>
</tr>
<tr>
<td>Thrombocytes (*10^3/uL)</td>
<td>238 (51.4, 384)</td>
</tr>
<tr>
<td>Peripheral blasts (percent)</td>
<td>16 (14, 31)</td>
</tr>
</tbody>
</table>
These two patients had the lowest gestational age and birth weight, had the highest level of blasts in the peripheral blood and a longer period for obtaining spontaneous remission (Table 2).

Five patients presented with AML and the mean age at diagnosis was 2.4 years. Two of them were diagnosed at birth with TL-DS based on hematological findings without any suggestive clinical signs. The onset of AML was marked by hepatosplenomegaly, bleeding disorders and fever. Laboratory investigations showed hyperleucocytosis (1/5 patients), anemia (2/5 patients), thrombocytopenia and peripheral blasts in all 5 cases. The immunophenotyping showed presence of megakaryoblasts in 4 cases and one case had biphenotyping acute leukemia. Besides trisomy 21 cytogenetics showed trisomy 11 (1/5 patients), hyperdiploidy (1/5 patients) and chromosomal structural anomalies (1/5 patients). One patient was positive for FLT3-ITD and NPM1A gene mutation. Remission was obtained in 2 cases, during the treatment protocol 2 patients died and one patient died in a context that was not directly related to AML therapy.

ALL-DS was diagnosed in 11 patients and the mean age at diagnosis was 4 years. None of these patients had TL-DS at birth. At the onset of ALL-DS, most patients presented pallor, hepatosplenomegaly, bleeding disorders, fever and bone pain. Laboratory tests showed hyperleucocytosis (1/11 patients), anemia (5/11 patients), thrombocytopenia (4/11 patients) and peripheral blasts (8/11 patients). Immunophenotyping showed common B-cell precursor ALL (9/11 patients) and Pre B ALL (2/11 patients). Besides the presence of trisomy 21, the cytogenetic tests showed also the presence of monosomy 8, X, trisomy 10,11, hyperdiploidy and chromosomal structural disorders. TEL/AML1 was positive in two patients and one of them was also positive for BCR/ABL. Four patients died during the treatment protocol, one was lost to follow up and the rest of the patients are in remission.

Because CD20 and CD45 markers were the most heterogeneous in our cases, we analyzed their influence on the disease features. CD20 was found only in ALL-DS cases (Figure 1) and CD45 was expressed only in 28.5% of ALL-DS cases, including common B-cell precursor and Pre B ALL-DS. In AM-DSL cases and in the case of biphenotyping acute leukemia, CD45 had a more frequent expression (75%). Moreover, CD45 positive cases had more severe anemia (p=0.246) and thrombocytopenia at the onset (p=0.234) (Figure 2).

Comparing the ALL-DS cases with the ones with AML-DS it was observed an older age for the
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onset of ALL-DS (p=0.00083). This was not correlated with the type of ALL-DS. Taking into consideration only the cases with ALL-DS and the presence of CD20 we observed that there was a tendency for CD20 positive in older age (p=0.149) and was not correlated to the type of ALL-DS (p=0.0428) (Table 3). It appears that the more aggressive entity at presentation was represented by CD45 positive leukemia, which is the more frequent of the myeloid lineage and has lower counts at diagnosis.

Discussion

AML represents 20% of acute leukemia cases in pediatric patients [35]. About 9% of the AML cases or myelodysplastic syndromes appear in patients with DS [36]. AML versus ALL ratio in patients with DS is reported to be 1:1. AML-DS has a higher incidence under the age of 4 and ALL-DS tends to appear more frequent in older age [37]. In the case series presented earlier, we found a significant difference between AML-DS and ALL-DS regarding the age at the diagnosis, with AML-DS having a preponderance for younger age.

Many cases of TL-DS are asymptomatic and have spontaneous remission, but the identification of this condition in newborns with DS is important because of the increased risk of developing acute leukemia. Using WHO definition for TL-DS based on clinical criteria [10], many asymptomatic cases are not diagnosed during the neonatal period. Moreover, in some cases, spontaneous remission

Figure 2. Platelet count and hemoglobin value depending on the immunophenotype.

Table 3. Statistical analysis between AML and ALL for the main hematology and flow cytometry parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CD20</th>
<th>CD45</th>
<th>AML vs ALL (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.149</td>
<td>0.350</td>
<td>0.0083</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>0.628</td>
<td>0.556</td>
<td>0.177</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1</td>
<td>0.246</td>
<td>0.949</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>1</td>
<td>0.254</td>
<td>0.394</td>
</tr>
<tr>
<td>Peripheral blasts</td>
<td>0.628</td>
<td>0.854</td>
<td>0.599</td>
</tr>
<tr>
<td>Bone marrow aspirate blasts</td>
<td>0.153</td>
<td>0.589</td>
<td>0.432</td>
</tr>
</tbody>
</table>
can appear before birth. In some cases, the hematological disorders with the presence of peripheral blasts were found accidentally by performing investigations for other reasons [14,24,58]. Regarding the patients identified in Romania, only two AML-DS cases were diagnosed with TL-DS in the neonatal period. TL-DS diagnosis could be improved by a newborn screening program including, besides the clinical criteria, and the presence of more than 10% blasts in the peripheral blood smear, and also the presence of GATA1 mutation [12,14,18]. The sensitivity and specificity of more than 10% blasts in the peripheral blood smear for the presence of GATA1 mutation is 74% and 81%, respectively [39].

The most common clinical findings in symptomatic patients with TL-DS are hepato-splenomegaly, serositis and bleeding disorders [40,41]. Moderate or severe hepatomegaly is found in 50-60% of the cases, splenomegaly in 36-44% of the cases [42] and serositis, especially pericarditis with heart failure, is more common in patients with DS and congenital heart malformations [15]. In the case series presented earlier, hepatosplenomegaly was found in 40% of the cases and pericarditis with signs of heart failure in one patient with an associated congenital interventricular septal defect. Risk factors for a bad prognosis in patients with symptomatic TL-DS are gestational age under 37 weeks and increased level of leucocytes [43]. Massey et al showed in a meta-analysis that early death appeared in 17% of newborns with TL-DS and was correlated with high levels of leucocytes, bilirubin and liver enzymes [14]. Gamis et al also showed that the mortality rate in TL-DS was 9-10% and was correlated with hepatomegaly, leucocytosis and black race. Thromocyte level, percent of peripheral blasts higher than in the bone marrow, splenomegaly, gestational age, and associated heart malformations did not influence the mortality rate [15]. From our cases, two patients had a gestational age under 37 weeks, one of them also associated with increased level of leucocytes, without any other signs or symptoms suggestive for a bad prognosis, and both patients needed a longer period of time until obtaining spontaneous remission, but no longer than 3 months.

There is no evidence yet for a correlation between the severity of the symptoms in TL-DS and the progression to AML-DS. Moreover, there is no evidence that TL-DS treatment can prevent the progression to AML-DS. At this moment the treatment is indicated only in the presence of life-threatening symptoms and not for eradication of blast cells [15,23,26,44]. Just one patient with TL-DS included in our study needed treatment because of heart failure.

The markers expressed on the surface of the blast cells in TL-DS are mostly the same like in AML-DS blasts, but with an increased frequency of CD54 [45] and the presence of stem cells markers like CD34, CD117, myeloid markers like CD33/CD13 and thrombocytes markers CD36, CD 42, CD 61 [46,47]. The patients with TL-DS from our study were positive for CD34 and CD117.

The malignant cells from TL-DS and the ones from AML-DS share the same mutation, GATA1. This mutation associated with trisomy 21 is considered pathognomonic for TL-DS and AML-DS. Besides this, the malignant cells from AML-DS seem to acquire other genetic anomalies. AML-DS has a different profile than AML in patients without DS, most frequent karyotype disorders are the trisomy 8,11, del(6q), del(7p), del(16q) and dup(1p) [48]. Moreover, none of the genetic disorders associated with a good prognosis like t(8;21), t(15;17), t(9;11) and inv(16) or t(1;22) and t(1;5) associated with AML do not appear in AML-DS [49]. In our AML-DS case series we found, besides trisomy 21, trisomy 11, hyperdiploidy and chromosomal structural disorders. One patient was positive for FLT3-ITD and NPM1A mutations.

The major difference between AML-DS and AML of patients without DS is the increased remission rate [20]. AML-DS has an event-free survival (EFS) rate of 80-100% and a relapse rate under 15% [50,51]. Patients with AML-DS are considered a subgroup that needs to be treated according to a protocol, particularly designed for them [50]. The reason for a good response to cytosine arabinoside treatment is the overexpression of cystatin-B-synthetase gene, localized on chromosome 21, which makes the malignant cells more susceptible to apoptosis [52]. Two of our patients, diagnosed with AML-DS died during the treatment protocol because of drug toxicity.

ALL-DS has a higher incidence after the age of 4 when the ratio ALL-DS: AML-DS is equal with the one in children without DS. There are some special features of ALL-DS, like high frequency in Caucasians, low incidence in young age and rare cases of ALL-DS with T-cells [53-56]. The mean age for the diagnosis of ALL in our case series was 4 years, without any correlation with the type of ALL (common B or pre B). Cytogenetic disorders with good prognosis like double trisomy 4 and 10, hyperdipoidy, ETV6-RUNX1 mutation, and the ones with a bad prognosis like BCR-ABL1 are less common in ALL-DS than in patients without DS [53-56]. Although our study included a small number of patients, we found disorders like trisomy 10,11 and BCR-ABL1 in one patient. The prognosis of cases with ALL-DS is reduced compared with the
prognosis of patients without DS, mostly because of high chemotherapy toxicity that needs dose reduction and increases the risk of relapse. Bone marrow transplant remains a treatment alternative for these cases, although there is little evidence regarding its efficiency in obtaining the remission and also for reducing the rate of relapse [54].

Regarding the surface markers, the intensity of CD45 and CD20 are independently correlated with outcome [57]. CD20 is an antigen that helps the differentiation of B cells and has different expressions in ALL with B precursors in children. The available evidence regarding the implication of CD20 in the prognosis of children with ALL has contradictory results. Some studies suggest that overexpression of CD20 is a risk factor for a bad prognosis [58], but this observation was not validated in other studies [59,60]. In adults, CD20 positive is correlated with hyperleucocytosis and a bad prognosis [61-74]. CD20 was identified in all cases with ALL-DS in our study, was not correlated with type of ALL-DS, leucocytosis, but we observed a trend of appearing at an older age.

CD45 is a surface marker specific for hematopoietic cells with increased expression in mature B cells, although it was identified also in ALL pro-B positive for MLL-AF4 mutation [75]. Cario et al have shown that overexpression of CD45 in ALL with T or B cell was correlated with hyperleucocytosis, bad response to chemotherapy, residual disease, and reduced EFS rate because of an increased rate of relapse [76]. In our study in all cases and, while not statistically significant (p=0.242), it appeared that ALL-DS generally did not express CD45 (both common ALL and preB ALL) (28.57%), while AML-DS and acute biphenotypic leukemia expressed it more often (75%). Moreover, there was a tendency for CD45 positive leukemia to have lower hemoglobin (p=0.246) and thrombocytes (p=0.234) level.

Conclusions

Acute leukemia of DS constitutes a special subgroup of pediatric malignancies and it has some interesting and yet, not well-defined particularities like the preleukemia state with spontaneous resolution, good response to treatment for AML-

DS diagnosed before the age of 4, but a negative outcome for ALL-DS with the onset at an older age. It appears that the more aggressive entity at presentation is represented by CD45 positive leukemia, which is more frequently of the myeloid lineage and has lower counts at diagnosis.

Although in Romania we have few statistical data regarding DS in general, our study is the first to present the baseline characteristics of the cases associated with TL-DS and/or acute leukemia. Patients were selected from the three main pediatric hematology centers from Romania, and the patient number is small, especially for TL-DS cases. This underlines the importance of diagnosing hematological disorders on newborns with DS and the need for a screening program including identification of GATA1 mutation in cases with a high suspicion of transient leukemia.

Children diagnosed with TL-DS in the neonatal period need closer monitoring regarding the hematologic disorder and the risk of developing acute leukemia, although there is no evidence yet regarding the management of TL-DS in order to reduce the risk of acute leukemia. Future studies need to clarify the pathogenetic mechanism of TL-DS and its apparent spontaneous remission and then progression to acute leukemia, nevertheless more evidence is needed regarding the management of TL-DS and acute leukemia of DS.

Acknowledgements

Valentina Sas and Cristina Blag contributed equally to the current manuscript. Valentina Sas was supported by an internal grant of the Iuliu Hatieganu University of Medicine and Pharmacy, School of Doctoral Studies (PCD 2019–2020). Ciprian Tomuleasa was supported from an ongoing grant of the Romanian Government: a National Research Grant awarded for Frontiers Research Projects (PN-III-P4-ID-PCCF-2016-112) awarded to the Babes Bolyai University in collaboration with the Ion Chiricuta Oncology Institute Cluj Napoca.

Conflict of interests

The authors declare no conflict of interests.

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JBUON 2020, 25(6): 2745


